In The United States Patent and Trademark Office

In re application of
Domenico FANARA et al.
Application No. 10/607,047 Art Unit: 1614
Filed: June 27, 2003 Examiner:

Declaration

I, Domenico FANARA, declare:

1. That I am an italian citizen, residing at Wanze (Belgium).
That I am a graduate of the University of Liège with the degree of pharmacist.
That I am an industrial pharmacist since 1989.
That I am in charge of research and development of new galenic formulations, in the Technical Development Department of UCB S.A., Brussels, since 1993.
That I am fully familiar with pharmaceutical technologies, i.e slow and controlled release formulations (coating, matrix tablets), taste masking technologies (coating, cyclodextrins ...), compression, extrusion, spheronization, development of emulsions, creams, capsules, syrups ...
That all the experiments mentioned below were carried out by myself or under my supervision in collaboration with Monique Berwaer, Pharmacist, Product Process Development Group Leader, of UCB S.A.

2. That the following study has been performed in 2003 (from June 11 to 25) under my supervision on the effect of soluble (sodium carbonate) and insoluble (Emcompress) alkaline agents on the dissolution of pseudoephedrine.

Pseudoephedrine tablets containing 120 mg doses and containing 16.1 % of Methocel K15M CR and 21.4 % of a diluent (lactose) or an alkaline agent (sodium

bicarbonate or Emcompress) were prepared by direct tabletting from homogeneous mixtures having the compositions presented In Table 1.

Table 1 – Composition of the A (batch 12630), B (batch 12634) and C (batch 12636) tablets

Constituents	*mg/tablet*		
	A	B	C
Pseudoephedrine.HCl	120	120	120
Methocel K15M CR	45	45	45
Sodium carbonate anhydrous	60	-	-
Emcompress	-	60	-
Lactose	-	-	60
Avicel pH 102	50.8	50.8	50.8
Aerosil 200	1.4	1.4	1.4
Magnesium stearate	2.8	2.8	2.8

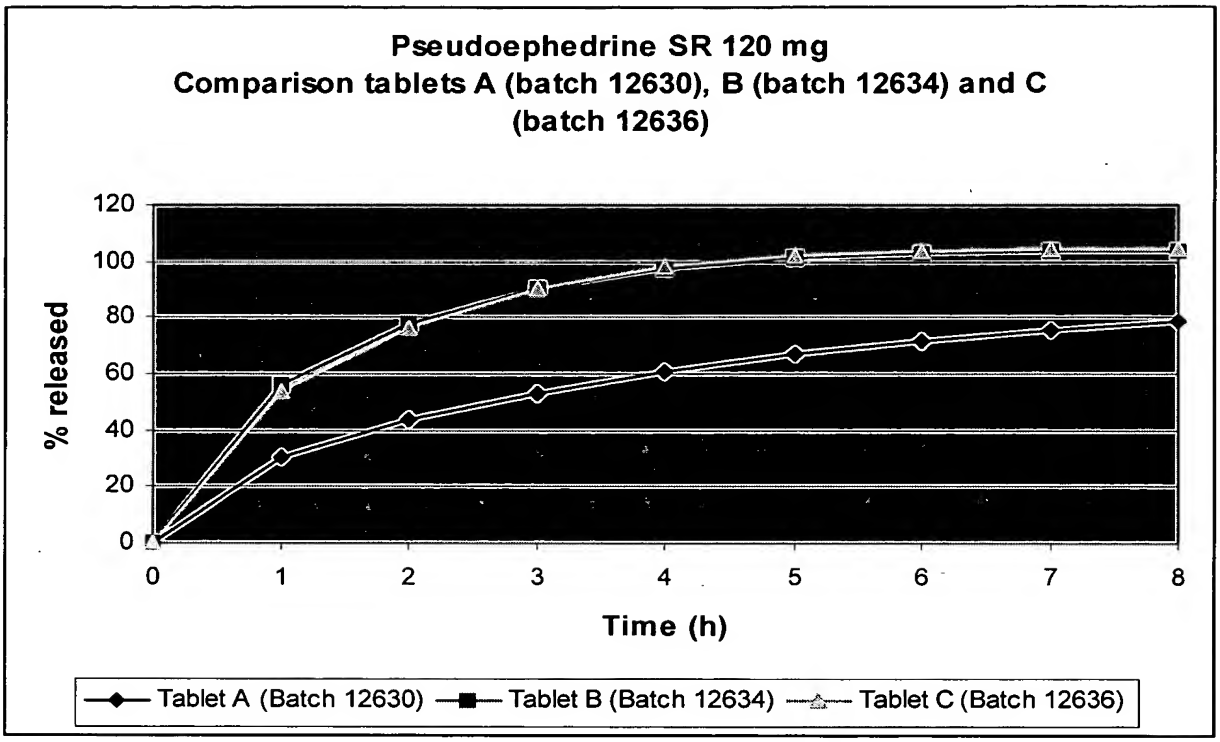
The kinetics of release of pseudoephedrine from these 3 types of tablets was determined with the aid of the USP 26 dissolution apparatus No. 1 (26th edition of the American Pharmacopoeia). The tablets were placed in the basket which was subjected to 50 revolutions per minute. The dissolution medium consists of distilled water kept at 37°C. Every hour, for 8 hours, a sample is taken from the dissolution medium and the pseudoephedrine is assayed by HPLC. The results of these assays are presented in Table 2.

Table 2 – Percentage release of pseudoephedrine

Time (h)	A	B	C
0	0	0	0
1	30.5	53.6	53.9
2	43.3	77.9	76.2
3	53.3	90.3	90.3
4	60.9	97.8	98.5
5	66.9	101.3	102.2
6	71.7	102.9	103.8
7	75.6	103.4	104.3

8	79.1	103.9	104.7

The results of Table 2 show that a prolonged release is obtained only with the tablet A containing a soluble alkalinizing agent. Tablets B and C rapidly release the active and both curves can be superimposed.



Calculation of the similarity factor f2 for the curves corresponding to the tablets A and B or C give a result of, respectively, 24.82 and 24.76 indicating the absence of similarity between the curve of tablet A and the curves of tablets B or C. On the contrary, curves corresponding to tablets B and C are similar (f2 = 89.81).

(Two curves are similar if 50< f2<100 and if the average difference at any dissolution sampling time point is not greater than 15 %).

Similar results were already obtained with a different percentage (14.3 %) of the diluent or the alkaline agents (soluble and insoluble).

3. That the following study has been performed in 2003 (from June 12 to July 2) under my supervision on the effect of soluble (sodium carbonate) and insoluble (Emcompress) alkakine agents on the dissolution of trapidil.

Trapidil tablets containing 300 mg doses and containing 33.3 % of Methocel K100M CR and 9.2 % of an alkaline agent (sodium bicarbonate or Emcompress) were prepared by direct tabletting from homogeneous mixtures having the compositions presented In Table 3.

Table 3 – Composition of the D (batch 12646) and E (batch 12648) tablets

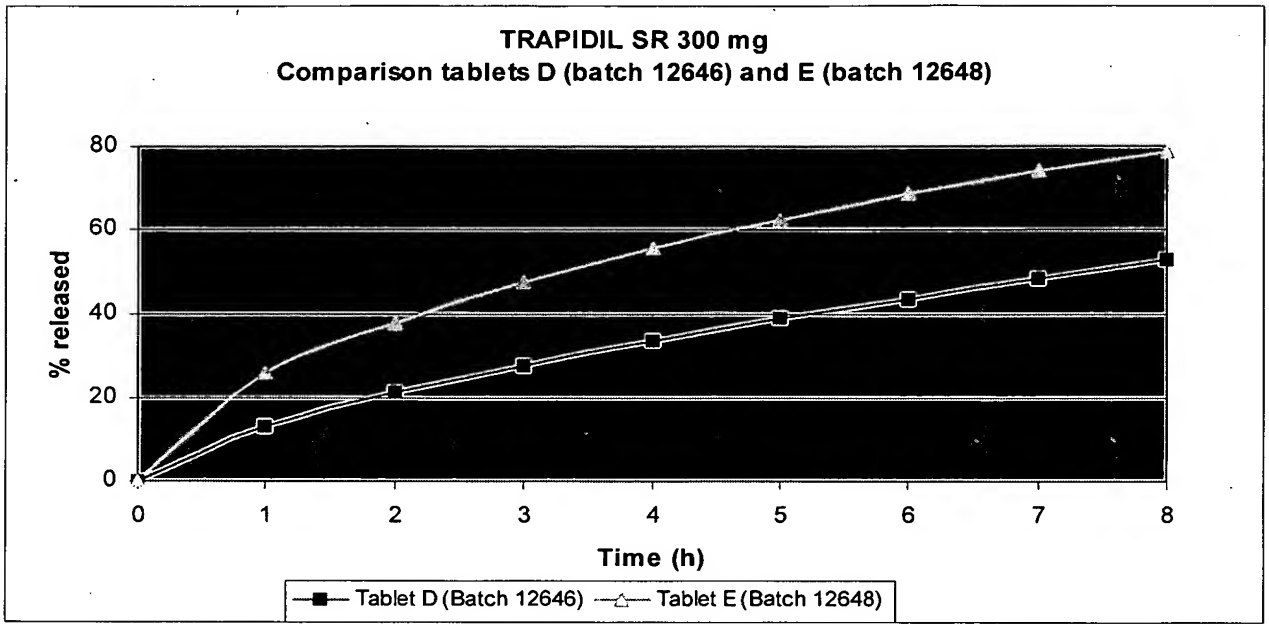
Constituents	*mg/tablet*	
	D	E
Trapidil	300	300
Methocel K100M CR	200	200
Sodium carbonate anhydrous	55	-
Emcompress	-	55
Avicel pH 102	36	36
Aerosil 200	3	3
Magnesium stearate	6	6

The kinetics of release of trapidil from these 2 types of tablets was determined with the aid of the USP 26 dissolution apparatus No. 1 (26th edition of the American Pharmacopoeia). The tablets were placed in the basket which was subjected to 100 revolutions per minute. The dissolution medium consists of a HCl 0.1 N solution kept at 37°C. Every hour, for 8 hours, a sample is taken from the dissolution medium and the trapidil is assayed by UV spectrophotometry. The results of these assays are presented in Table 4.

Table 4 – Percentage release of trapidil

Time (h)	D	E
0	0	0
1	13.2	25.6
2	21.1	37.7
3	27.4	47.6
4	33.3	55.7
5	38.7	62.5
6	43.6	68.6
7	48.3	74.1
8	52.9	78.9

The results of Table 2 show that a prolonged release is obtained only with the tablet A containing a soluble alkalinizing agent. Tablets B rapidly release the active.



Calculation of the similarity factor f2 for the curves corresponding to the tablets D and E gives a result of 32.85 indicating the absence of similarity between the curve of tablet D and the curve of tablet E.

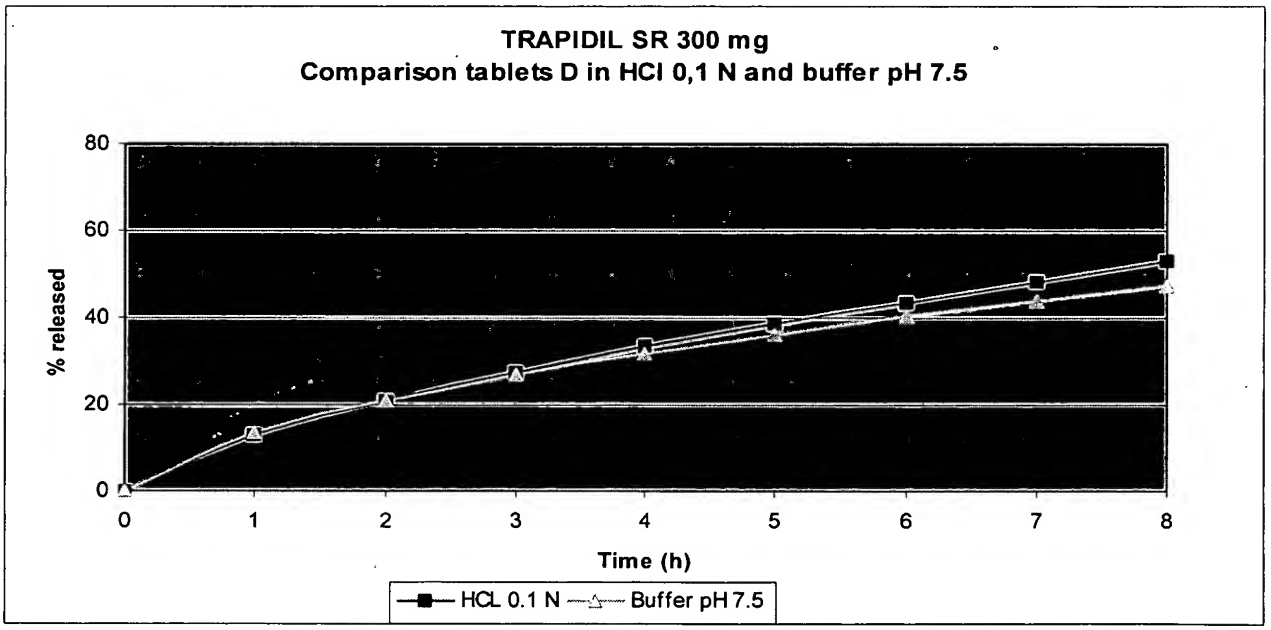
4. That the following study has been performed in 2003 (from June 12 to July 2) under my supervision on the influence of the pH on de dissolution of a tablet containing Trapidil and a soluble alkaline agent.

The kinetics of release of trapidil from tablets D were determined with the aid of the USP 26 dissolution apparatus No. 1 (26th edition of the American Pharmacopoeia). The tablets were placed in the basket which was subjected to 100 revolutions per minute. The dissolution media consist of a HCl 0.1 N solution and a phosphate buffer solution at pH 7.5 kept at 37°C. Every hour, for 8 hours, a sample is taken from the dissolution media and the trapidil is assayed by UV spectrophotometry. The results of these assays are presented in Table 5.

Table 5 – Percentage release of trapidil from tablets D

Time (h)	HCl 0.1 N	Buffer pH 7.5
0	0	0
1	13.2	13.4
2	21.1	21.0
3	27.4	26.9
4	33.3	31.7
5	38.7	36.1
6	43.6	40.3
7	48.3	44.0
8	52.9	47.5

There are no significant differences between both curves which can be pactically superimposed.

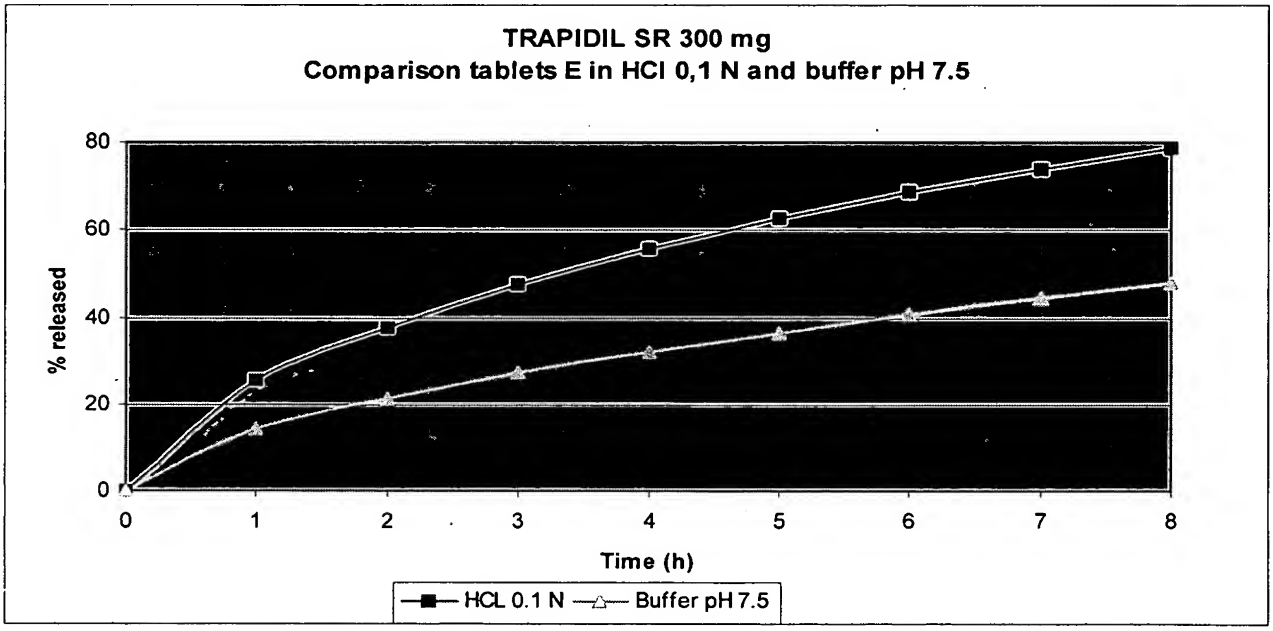


Calculation of the similarity factor f2 for the curves corresponding to the different media gives a result of 75.51 indicating the similarity between both curves.
The presence of the alkaline soluble agent permits to obtain a drug release independent of the pH. On the contrary, if tablet E is submitted to a dissolution test at pH 7.5 as described above the pharmacokinetics are quite different as seen in the table 6.

Table 6 – Percentage release of trapidil from tablets E

Time (h)	HCl 0.1 N	Buffer pH 7.5
0	0	0
1	25.6	14.2
2	37.7	21.3
3	47.6	27.1
4	55.7	32.1
5	62.5	36.3
6	68.6	40.6
7	74.1	44.5
8	78.9	48.1

Calculation of the similarity factor f2 for the curves corresponding to the different media gives a result of 30.84 indicating the absence of similarity between both curves.

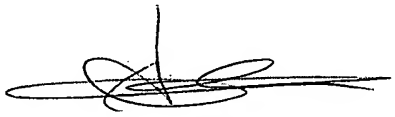


These results prove that a prolonged release independent of the pH as claimed in the patent application can be obtained only with the presence in the tablet composition of a soluble alkaline agent.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

31/08/2005

Date



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